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Review article

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Hepatic inflammatory responses in liver fibrosis

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Abstract

Chronic liver diseases such as nonalcoholic fatty liver disease (NAFLD) or viral hepatitis are characterized by persistent inflammation and subsequent liver fibrosis. Liver fibrosis critically determines long-term morbidity (for example, cirrhosis or liver cancer) and mortality in NAFLD and nonalcoholic steatohepatitis (NASH). Inflammation represents the concerted response of various hepatic cell types to hepatocellular death and inflammatory signals, which are related to intrahepatic injury pathways or extrahepatic mediators from the gut–liver axis and the circulation. Single-cell technologies have revealed the heterogeneity of immune cell activation concerning disease states and the spatial organization within the liver, including resident and recruited macrophages, neutrophils as mediators of tissue repair, auto-aggressive features of T cells as well as various innate lymphoid cell and unconventional T cell populations. Inflammatory responses drive the activation of hepatic stellate cells (HSCs), and HSC subsets, in turn, modulate immune mechanisms via chemokines and cytokines or transdifferentiate into matrix-producing myofibroblasts. Current advances in understanding the pathogenesis of inflammation and fibrosis in the liver, mainly focused on NAFLD or NASH owing to the high unmet medical need, have led to the identification of several therapeutic targets. In this Review, we summarize the inflammatory mediators and cells in the diseased liver, fibrogenic pathways and their therapeutic implications.

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Key points

- The liver harbours a dense network of phagocytes that maintain tolerance under non-inflammatory conditions and quickly sense hepatocyte stress and injury signals leading to the activation of pro-inflammatory cascades.
- Upon injury, leukocytes rapidly infiltrate the liver parenchyma, contributing to inflammation and fibrogenesis by producing soluble mediators that activate other immune cells and non-parenchymal cell populations.
- Inflammatory mediators can activate hepatic stellate cells (HSCs), the main effector cells during hepatic fibrogenesis, resulting in excessive extracellular matrix deposition as a wound-healing or scarring response.
- Production of pro-inflammatory mediators by activated HSCs, in turn, perpetuates hepatic inflammation, resulting in a chronic cycle of inflammation and formation of scar tissue, ultimately leading to organ failure.
- Current technological advances have led to an unprecedented comprehensive understanding of the hepatic inflammatory processes underlying fibrogenesis, resulting in the identification of novel potential anti-inflammatory and antifibrotic targets.
- Treatment of the underlying liver disease seems the most effective antifibrotic strategy, but developing efficient therapies remains challenging as preclinical results rarely translate to human disease in clinical trials.

Introduction

Hepatic fibrosis is a result of chronic inflammation and is a common consequence of various liver diseases, including viral, toxic, metabolic and autoimmune diseases. It occurs after years or decades of constant or repetitive organ damage with a persisting immune response and is characterized by an increase in and changed composition of extracellular matrix (ECM) with deposition of collagen and other fibrillar proteins such as elastin in the space of Disse[1]. If too much ECM is produced, the liver architecture is disrupted, which impairs organ function, alters intrahepatic blood flow and might progress to liver cirrhosis. Inflammation and fibrosis are closely interlinked, as evidenced in many chronic liver diseases. For example, persistent inflammation, as seen in untreated viral hepatitis or nonalcoholic fatty liver disease (NAFLD), promotes progressive ECM deposition over time, which is associated with long-term outcomes such as liver failure, hepatocellular carcinoma and mortality[2–4]. Conversely, successful antiviral therapy in individuals with chronic viral hepatitis[5,6] or substantial lifestyle modification in those with nonalcoholic steatohepatitis (NASH) can promote the resolution of fibrosis[7,8]. This clinical observation provides evidence of the dynamic nature of hepatic fibrosis, in which inflammatory processes not only initiate and perpetuate fibrogenesis but might also promote fibrolysis and fibrosis regression[9].

Among the first mediators released during acute inflammation are antifibrotic factors that induce blood clotting and matrix metalloproteinases (MMP) that degrade ECM to alleviate infiltration of immune cells[10]. When inflammation subsides, phagocytes clean up the debris, releasing anti-inflammatory mediators[11]. This process leads to the attraction of endothelial cells, blood vessel growth and activation of tissue macrophages and myofibroblasts to rebuild and reform the ECM, eventually closing the wound. Hepatic stellate cells (HSCs) have been shown to be the main producers of ECM during hepatic fibrogenesis[12], although other cellular sources contribute to ECM synthesis in liver fibrosis[13]. In the resting liver, HSCs metabolize and store retinoids and are responsible for the turnover of the ECM. Upon activation by profibrotic stimuli, HSCs transdifferentiate into myofibroblasts[14], lose their vitamin A, upregulate α-smooth muscle actin (αSMA) and start to produce collagens and inhibitors of matrix degradation. During this process, normal parenchyma is replaced by connective tissue to maintain organ integrity and function. However, activated HSCs also produce pro-inflammatory cytokines and chemokines that will recruit immune cells to the injured liver, thereby perpetuating inflammation[15]. This interplay of immune cell recruitment and wound healing processes can result in a chronic cycle of inflammation and regeneration that cannot be resolved, and normal tissue is replaced with non-functional scar tissue, which disturbs organ architecture and might lead to organ failure[16].

Although these principles have been known for decades, studies combining omics technologies with resolution at the single-cell level have provided new insights into the concerted interplay of injury signals, immune cells and fibrogenic pathways in the liver. In the following paragraphs, we provide a comprehensive overview of the key principles of inflammation and fibrosis, emphasizing current findings on immune and mesenchymal cell heterogeneity, mechanisms of cellular crosstalk and potential targets for therapeutic interventions.

Inflammatory processes modulating fibrogenesis

Inflammatory mediators

Danger signals released from dying cells. Damaged and dying cells release soluble mediators that act as damage-associated molecular patterns (DAMPs) or alarmins to alert surrounding cells to the tissue injury. In the liver, dying hepatocytes have been shown to release $P2Y_{14}$ ligands, such as uridine 5′-diphosphate (UDP)-glucose and UDP-galactose, that bind to the $P2Y_{14}$ receptor on HSCs and directly induce activation in both mouse and human HSCs[17]. Accordingly, $P2Y_{14}$ deficiency resulted in reduced fibrosis in several preclinical mouse models[17]. Similarly, the nuclear protein high-mobility group box 1 (HMGB1) can be released by damaged hepatocytes and directly activate HSCs[18]. Mitochondria-derived DAMPs (mito-DAMPs), which consist mainly of mitochondrial DNA sharing similarities with bacterial DNA, are also very abundant in the liver as hepatocytes contain high numbers of mitochondria due to their high metabolic activity[19]. Mito-DAMPs are increased in patients with NASH and fibrosis, and induce activation of HSCs and scar tissue formation in preclinical mouse models[20].

Parenchymal and non-parenchymal cell populations in the liver (including HSCs, sinusoidal endothelial cells and Kupffer cells (the resident liver macrophages)) can sense the release of these danger signals, for example, via pattern recognition receptors. One key response is the formation of inflammasomes, which are evolutionarily conserved protein complexes assembled by cellular stressors and specific signalling events, that initiate inflammatory responses by processing IL-1β, releasing IL-18 and eventually promoting inflammatory cell death (that is, pyroptosis)[21].

IL-33 is an alarmin related to T helper 2 (T_H2) cytokine responses and is released by stressed hepatocytes in human and mouse fibrosis.

This IL-33 release triggers the recruitment of group 2 innate lymphoid cells (ILC2s), which in turn activate HSCs through the production of IL-13 (ref. 22). Furthermore, IL-33 can also act on HSCs directly and stimulate the production of matrix proteins[23].

In cholestatic liver diseases, bile acids accumulate in human and mouse tissue and can drive inflammation by inducing the production of pro-inflammatory mediators such as chemokines, cytokines and adhesion molecules in hepatocytes and other cells[24]. Several non-parenchymal hepatic cells, including HSCs and macrophages, can sense pathogenic bile acids (for example, via the receptor TGR5 (also known as GPBAR1))[25] and might subsequently promote fibrogenic responses such as cholangiocyte proliferation and ductular reaction[26].

Extrahepatic signals. Liver inflammation is substantially modulated by extrahepatic mediators derived from other sites such as the gut or adipose tissue. This is particularly evident in NAFLD and NASH, where nutritional factors, microbial metabolites, and gut and adipose tissue hormones affect liver disease progression[27]. The gut–liver axis is altered in many pathological conditions and can drive liver disease as the gut and liver form an anatomically and functionally linked unit[28]. If intestinal homeostasis is affected, bacterial metabolites, pathogen-associated molecular patterns (PAMPs), bile acids and nutrient components reach the liver via the portal vein[29]. Microbial products such as lipopolysaccharide are elevated in many liver diseases, indicating increased gut permeability, and induce a pro-inflammatory response mostly mediated by liver-resident macrophages[28]. Alterations in nutrients such as fatty acids and bacterial metabolites such as ethanol can also drive liver inflammation[29–31]. Furthermore, the composition of bile acids changes with intestinal dysbiosis, as gut bacteria modify secondary bile acids before being recycled to the liver[32]. If fewer primary bile acids reach the small intestine, pro-inflammatory bacteria overgrow other species, and the associated increase in toxic bile acids exacerbates liver cell damage and inflammation[33]. By contrast, activation of the nuclear receptor farnesoid X receptor (FXR) in hepatocytes by distinct (endogenous or synthetic) bile acids prevents the upregulation of inflammatory response genes and promotes cell survival[34]. Thus, the consequences for liver inflammation and fibrosis depend on the exact composition of the bile acid pool, which is closely connected to alterations in the gut microbiome.

In metabolic liver disease, adipose tissue-derived signals can also contribute to disease progression. In individuals with obesity, the flux of free fatty acids from adipose tissue to the liver is increased, contributing to lipotoxicity and subsequent inflammation, which is even more pronounced in the presence of insulin resistance[35]. In turn, the liver can also send signals to the adipose tissue to increase lipolysis, further exacerbating this cycle[36]. In addition, adipose tissue-derived leptin has been shown in mice to activate liver-resident macrophages and increase their responsiveness to endotoxin, leading to increased hepatic inflammation[37,38]. Leptin-activated Kupffer cells also induce HSC activation in vitro, suggesting (indirect) profibrogenic properties as well[39].

Chemokines and chemokine receptors. Chemokines (or chemoattractant cytokines) coordinate the recruitment and positioning of immune cells in injured livers[40]. Among the first chemokines released following liver injury are CCL2, CCL3, CCL5, CXCL9 and CXCL10, which recruit monocytes via CCR2 (and CCR5), and T cells via CCR5 and CXCR3. The profibrogenic role of the CCL2–CCR2 pathway is emphasized by the fact that *Ccr2*$^{-/-}$ mice develop significantly ($P < 0.05$) less fibrosis than wild-type mice[41,42]. Accordingly, pharmacological inhibition of CCR2 ameliorates hepatic inflammation and fibrosis and prevents infiltration of CCR2^{+} monocytes in mouse models of NASH[43]. Deficiency or antagonism of CCL3 and CCL5 also reduces immune cell infiltration and fibrosis development in mouse models, suggesting a similar profibrogenic role for these chemokines[44,45]. By contrast, the fractalkine receptor CX_3CR1 limits hepatic fibrogenesis in vivo[46] by limiting infiltration and controlling the differentiation and survival of intrahepatic monocytes[47].

The roles of CXCR3, and its ligands CXCL9, CXCL10 and CXCL11, are more complex, as this pathway is involved in the recruitment of various lymphocytes. Both intrahepatic and peripheral levels of CXCL9 and CXCL10 increase upon liver injury and are associated with disease severity in patients with varying degrees of fibrosis[48,49]. Preclinical studies have shown conflicting functions for this chemokine axis, as CXCR3-deficient mice are less susceptible to steatohepatitis induction than wild-type mice but develop more severe fibrosis upon toxic liver injury[50,51]. These opposing roles might at least partly be explained by the fact that CXCR3 is involved in recruiting pro-inflammatory and anti-inflammatory T cell subsets, including T_H1 cells and regulatory T (T_{reg}) cells[52,53].

CXCR6 and its ligand CXCL16 are involved in recruiting natural killer T (NKT) cells and other lymphocytes upon liver injury. CXCR6-deficient mice show reduced accumulation of NKT cells and are protected from liver fibrosis progression in different models of experimental fibrosis[54]. Pharmacological inhibition of CXCL16 has the same effect on fibrosis and reduces macrophage infiltration and intrahepatic levels of pro-inflammatory cytokines[55]. However, CXCR6^{+} NKT cells exert critical antitumour effects in mouse models[56,57], highlighting their dual role in chronic liver diseases. Importantly, CXCR6 is not specific to NKT cells but is present in several lymphocyte populations, including liver-resident CD8^{+} T cells in NASH that trigger auto-aggression against hepatocytes[58] and show dysfunctional tumour surveillance in mouse models of NASH[59].

CCL20 is upregulated in mouse models and patients with chronic liver diseases and correlates with disease severity[60]. It is produced by both parenchymal and non-parenchymal cells, and recruits a subset of γδ T cells via CCR6, which limits fibrosis by inducing apoptosis of activated HSCs[61].

Other chemokine receptor pathways involved in immune cell recruitment to the injured liver include CCR7–CCL21 and CXCR4–CXCL12. Upregulation of the ligands is commonly seen in many liver diseases, but as these receptors are expressed by various cell types — including lymphocytes, myeloid cells and stem cells — their exact role in liver pathology highly depends on the disease context[62–64].

Hepatic immune cells

Even during homeostasis, the liver tissue is scattered with immune cells that are distributed throughout the parenchyma but enriched in periportal regions[65]. The zonation of immune cells in the liver is not only organized by hepatic signals related to hepatocyte homeostasis and endothelial cell signals[66], but also affected by extrahepatic cues such as microbial metabolites from the gut–liver axis[67]. A major function of a dense network of phagocytes, the liver-resident Kupffer cells, is the scavenging of pathobionts (for example, Gram-positive bacteria) via the complement receptor of immunoglobulin superfamily (CRIg; also known as VSIG4)[68]. Several non-parenchymal and immune cells, such as Kupffer and dendritic cells, are capable of antigen presentation, primarily maintaining tolerance under non-inflammatory conditions[69]. Liver lymphocytes include conventional and unconventional T cells, ILCs and

B cells[70]. Upon injury, damaged cells rapidly produce inflammatory mediators, among them chemokines and cytokines that will recruit leukocytes to the site of injury (Fig. 1). The first cells to arrive in damaged areas are neutrophils and monocytes and/or macrophages, which can clear up dead cells and debris, and lymphocytes, which produce cytokines and other mediators that will, in turn, activate macrophages and fibroblasts and perpetuate inflammation.

Monocytes and macrophages. Hepatic macrophages, that mainly comprise tissue-resident Kupffer cells and monocyte-derived macrophages (MoMFs), are characterized by a high phenotypic and functional diversity and plasticity[11,71,72]. They play a key role during inflammation, injury and fibrogenesis[43,73] but can also promote fibrosis resolution[74]. Kupffer cells act as intravascular sentinels[72] that sense hepatocyte stress and injury signals from other cells (or extrahepatic sources), engulf cellular debris and can activate inflammatory signals[40,75]. In inflammatory settings, the pool of liver macrophages is augmented by a robust influx of bone marrow-derived monocytes that give rise to MoMFs. MoMFs are functionally and phenotypically distinct from Kupffer cells, but mouse models indicate a remarkable plasticity between the two lineages[66,71]. A series of elegant studies using single-cell RNA sequencing (scRNA-seq) have provided unprecedented insights into hepatic myeloid cell heterogeneity[72,73,76,77]. One key observation is that MoMFs can replace Kupffer cells and acquire a phenotype of 'lipid-associated macrophages' or 'scar-associated macrophages' (SAMs), including TREM2, CD9 and osteopontin expression[78–80]. Although many of these

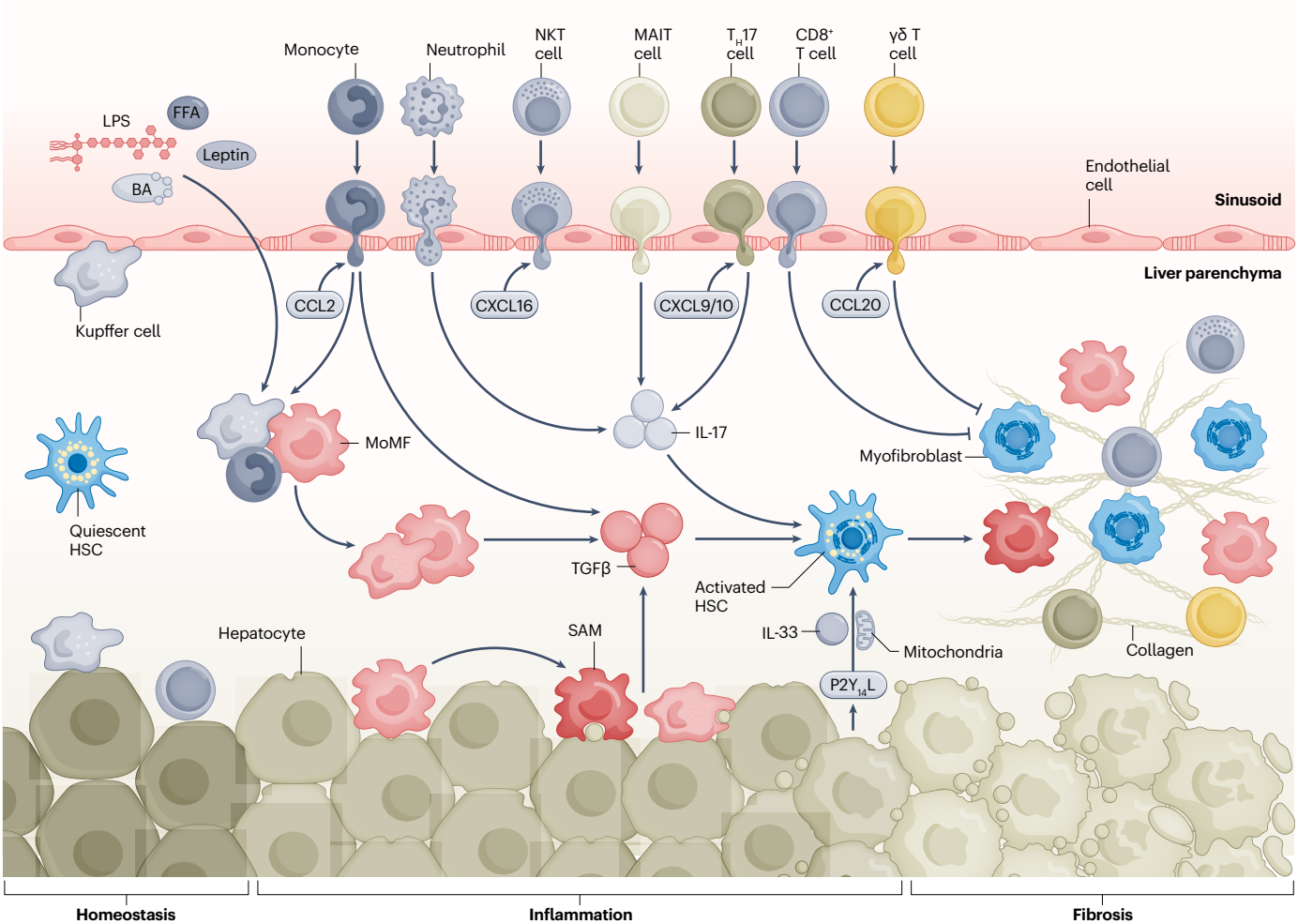

Fig. 1 | Inflammatory processes modulating fibrogenesis. In homeostasis, immune cells are scattered in the liver, especially resident macrophages (Kupffer cells) that serve as intravascular sentinels. They quickly react to a perturbation in extrahepatic signals — such as bile acids (BAs) and bacterial metabolites (for example, lipopolysaccharide (LPS)) from the gut and lipid mediators (such as free fatty acids (FFA) and leptin) from the adipose tissue — and hepatocyte injury, triggering a pro-inflammatory response. Among the first circulating immune cells to arrive in the liver after injury are monocytes, recruited via CC-chemokine ligand 2 (CCL2), that produce profibrogenic mediators such as transforming growth factor-β (TGFβ) and differentiate into monocyte-derived macrophages (MoMFs) that further perpetuate inflammation. Neutrophils also arrive early during inflammation and contribute to fibrogenesis through the production of IL-17, which activates hepatic stellate cells (HSCs). Auto-aggressive $CD8^+$ T cells further promote hepatocyte death. Danger signals (for example, $P2Y_{14}$ ligands ($P2Y_{14}L$)) and alarmins (such as IL-33 or mitochondrial metabolites) released by damaged hepatocytes further increase HSC activation. Lymphocytes are recruited via several chemokines, including CXC-chemokine ligand 16 (CXCL16) (natural killer T (NKT) cells), CXCL9 and CXCL10 (conventional T cells) and CCL20 (γδ T cells). T helper 17 (T_H17) cells and mucosal-associated invariant T (MAIT) cells increase fibrosis through the production of IL-17, although (some) $CD8^+$ T cells, γδ T cells and natural killer cells limit fibrogenesis through apoptosis induction in myofibroblasts. SAM, scar-associated macrophage.

discoveries have been primarily based on mouse models, scRNA-seq analyses of human liver tissue have identified the SAMs as a unique population located in the fibrotic niche of cirrhotic liver[76], and spatial proteogenomics analyses have confirmed conservation of this type of macrophage across several species[65]. Strikingly, the accumulation of inflammatory MoMFs in portal areas, particularly around ductular reactions, is a key feature characterizing advanced fibrosis in human liver biopsy samples across aetiologies[81].

Dendritic cells. Dendritic cells that connect innate and adaptive immunity consist of different subsets, mainly conventional (classical) dendritic cells (cDC1s and cDC2s) and plasmacytoid dendritic cells (pDCs). Mature dendritic cells are expanded in fibrotic livers[82], but their exact role in hepatic fibrogenesis is complex. Although several mouse studies have demonstrated that depletion or inhibition of dendritic cell maturation results in reduced inflammation and, therefore, reduced fibrosis in the liver[83,84], others have found that dendritic cell depletion does not influence fibrogenesis[85]. In addition, it has also been reported that dendritic cells can limit inflammation and fibrogenesis in mouse models of liver fibrosis[86,87]. Although cDC1, particularly their CD103$^+$ subtype, were initially described as a protective subtype under conditions of metabolic injury in mice[88], more current evidence suggests that cDC1s might have a pathogenic role in liver disease. In the context of NAFLD, they are abundantly found in both patients with NASH and mouse models of steatohepatitis, and their presence correlates with disease severity and fibrosis score[89]. In mouse models, XCR1$^+$ cDC1s promote inflammatory T cell reprogramming, thereby aggravating liver pathology[89].

Neutrophils. Neutrophil infiltration can be observed in all types of chronic liver disease, and they can contribute to hepatic inflammation through the production of inflammatory cytokines, activation of Kupffer cells and recruitment of other immune cells[90–93]. However, they do not seem to contribute to fibrogenesis directly[94]. Evidence from mice suggests that neutrophils are critical during the resolution phase of liver inflammation and fibrosis. They induce a functional switch in macrophages from pro-inflammatory to restorative phenotypes, an effect that is completely lost when neutrophils are depleted[95].

Mast cells. Mast cells are innate myeloid cells with a predominant role in allergies and autoimmune diseases. The healthy liver harbours only meagre numbers of mast cells, but infiltration of mast cells can be seen in liver diseases of almost all aetiologies, and their function seems to be mostly profibrogenic[96,97]. In a mouse model of NAFLD and NASH, increased numbers of mast cells are associated with enhanced inflammation and fibrosis, whereas depletion of mast cells reduces liver injury[98]. Similar effects can be observed in mouse models of cholestatic liver disease[99,100]. In patients with alcoholic or viral hepatitis, the number of infiltrating mast cells also correlates with fibrosis severity[101,102]. Histamine is one of the main mediators released by activated mast cells, and histamine signalling seems to be a key mechanism in mast cell-induced inflammation and fibrogenesis, as both inhibition of histamine and blockade of histamine receptors reduce liver damage and fibrosis in cholestatic injury mouse models[103,104].

B and T lymphocytes. Conventional T and B cells are the primary effector cells of the adaptive immune system and are critical for host immunity, clearance of pathogens and upkeep of self-tolerance. In the healthy liver, they reside mainly around portal tracts but frequently infiltrate the parenchyma during inflammation[105]. Adaptive immune cells have a major role in antigen-driven liver diseases such as autoimmune hepatitis and chronic viral hepatitis. In chronic hepatitis B virus (HBV) infection, for instance, insufficient priming of CD8$^+$ T cells by hepatocytes typically leads to T cell dysfunction[106], which can be overcome by Kupffer cell-mediated cross-presentation[107], as shown in mice. Although these inflammatory mechanisms drive fibrogenesis via hepatocellular cytotoxicity, adaptive immunity can also be involved in liver fibrosis independently of specific antigens[108]. This unspecific activation seems to be of particular relevance for NAFLD because mediators released during metabolic injury, including acetate and extracellular ATP, can trigger sustained auto-aggression against hepatocytes by liver-resident CXCR6$^+$PD1$^+$perforin$^+$CD8$^+$ T cells in an MHC-class-I-independent fashion, thereby driving steatohepatitis progression[58].

B cells only make up a small proportion of hepatic immune cells (only about 5% of intrahepatic lymphocytes in a healthy human liver)[109], but infiltration of B cells is observed in chronic liver diseases[108,110]. Little is known about the functional contribution of B cells to hepatic fibrogenesis, but evidence from mouse models suggests a profibrotic role. B cells accumulating in the injured liver display an activated phenotype and produce pro-inflammatory cytokines, and B cell-deficient mice fail to develop fibrosis in both toxic and diet-induced models[110–112]. Current evidence from mouse models and patients with NASH suggests that intestinal B cells promote hepatic fibrosis via immunoglobulin A secretion and activation of Fcγ receptor signalling on myeloid cells[113]. Interestingly, some B cell subsets, such as IL-10-producing regulatory B cells, might also have protective effects during NAFLD-associated liver inflammation and fibrosis[112].

In the context of T_H cells, liver fibrosis is strongly linked to T_H2 and T_H17 cell responses. The T_H2 cytokines IL-4 and IL-13 have profibrogenic functions as they can activate fibroblasts and stimulate ECM remodelling[114–118], whereas the T_H1 cytokines IL-12 and IFNγ have a rather antifibrotic effect[119]. T_H17 cells drive liver fibrosis via the production of IL-17 and IL-22, which stimulate transforming growth factor-β (TGFβ) production in the liver, enhance TGFβ signalling in HSCs, and induce the production of collagen by HSCs and pro-inflammatory cytokines by both HSCs and Kupffer cells[120–122]. Furthermore, mice deficient in the IL-17 or IL-22 receptor are resistant to fibrosis development, and IL-17 depletion in vivo can prevent fibrosis progression[120,121,123]. Importantly, IL-22 can also have protective functions in hepatic injury. IL-22 agonism improves liver inflammation in mice with acute-on-chronic liver failure[124], protects hepatocytes from injury during acute hepatitis[125] and reduces liver fibrosis in carbon tetrachloride (CCl_4)-treated mice through induction of HSC senescence[126]. In a phase II clinical trial, the IL-22 agonist F-652 reduced hepatic inflammation and increased regeneration in 18 patients with severe alcoholic hepatitis[127].

T_{reg} cells can inhibit hepatic fibrogenesis by producing the anti-inflammatory cytokine IL-10. IL-10 signalling suppresses the synthesis of collagen I[128], inhibits Kupffer cell activation[129] and limits IL-17 production by T_H17 cells leading to reduced HSC activation[123]. Consistently, *Il10*-knockout mice are more susceptible to liver fibrosis development[130]. However, T_{reg} cells can also restrict fibrosis resolution in mice by inhibiting MMP production by Kupffer cells, contributing to fibrosis persistence[131].

Data on the role of CD8$^+$ cytotoxic T cells in hepatic fibrosis is somewhat contradictory, which might be related to the coexistence of auto-aggressive and protective T cell immunity[58]. In a mouse model of toxic liver fibrosis, depletion of CD8$^+$ T cells did not influence

fibrogenesis[132], but the adoptive transfer of splenic $CD8^+$ T cells in the same model aggravated disease severity[133]. On the other hand, in a mouse model of obesity-induced NASH, depletion of $CD8^+$ T cells ameliorated liver inflammation and reduced HSC activation[134]. In this context, $CD8^+$ T cells were able to activate HSC directly. In addition, tissue-resident $CD8^+$ T cells with a memory phenotype were shown in mice to promote liver fibrosis resolution by inducing apoptosis of activated HSC[135]. Here, depletion of $CD8^+$ T cells impaired fibrosis resolution, whereas adoptive transfer of these cells prevented fibrosis progression. These conflicting data indicate that different subsets of $CD8^+$ T cells might be involved in liver fibrosis progression and resolution.

Unconventional T cells. Unconventional T cells are a heterogeneous group of lymphocytes that are abundant in the liver (they represent the majority of intrahepatic T cells but only 10% of T cells in the blood). The most important subsets of unconventional T cells include NKT cells, mucosal-associated invariant T (MAIT) cells and γδ T cells[136].

NKT cells seem to have a dual role in liver fibrosis. They can promote liver fibrosis through the production of profibrotic cytokines such as IL-4 and IL-13 (refs. 54,137), but it has been shown that they can also inhibit fibrosis by producing IFNγ and killing HSCs under specific conditions[138]. NKT cells influence fibrogenesis directly and can also polarize towards antifibrotic T_H1 and profibrotic T_H2 cell responses by releasing cytokines such as IFNγ and IL-4, respectively.

Our understanding of the role of MAIT cells in the liver is still evolving. Early studies in mice and patients with NAFLD indicated a protective role in NAFLD through the production of regulatory cytokines and polarization of macrophages towards an anti-inflammatory phenotype[139]. However, current experimental evidence indicates that MAIT cells have profibrogenic functions in chronically injured liver, as they can induce HSC activation via IL-17 or promote pro-inflammatory polarization of macrophages, and MAIT cell-deficient mice are resistant to fibrosis development[140,141]. Furthermore, inhibition of MAIT cell activation accelerates fibrosis resolution by promoting a restorative phenotype in monocytes and macrophages, as shown in humans and mice[142].

Importantly, NKT cells are much more abundant in mouse livers than in human livers, whereas MAIT cells are more frequent in human livers[70,143]. Given this opposing distribution, findings about NKT cells from mouse models need to be interpreted with caution, and MAIT cells have been suggested to be the human counterpart of NKT cells from a functional perspective[70,144].

Finally, γδ T cells have been shown to accumulate in fibrotic livers, but evidence of their exact role in hepatic fibrogenesis is sparse. Although they can contribute to hepatic IL-17 production in mouse models of liver fibrosis[121,145], which would suggest a profibrogenic function, they are also able to induce apoptosis of activated HSCs and increase natural killer cell-mediated cytotoxicity against activated HSCs, thereby limiting fibrosis progression[61,146].

Innate lymphoid cells. ILCs consist of several subsets, mainly natural killer cells, ILC1, ILC2, ILC3 and lymphoid tissue inducer cells[147]. Liver ILCs account for a substantial proportion of intrahepatic lymphocytes and comprise mostly group 1 ILCs, which include natural killer cells and tissue-resident ILC1s[148]. Data on the role of ILCs in the pathogenesis of liver fibrosis is emerging and partially controversial. Natural killer cells are frequently associated with protective functions during fibrogenesis in mice and humans as they can kill activated HSCs through cell lysis and induction of apoptosis and produce the antifibrotic cytokine IFNγ[149–152]. These effects promote the resolution of the ECM and balance towards T_H1-type responses. However, additional studies have shown that this protective function might critically depend on the subtype of natural killer cells or disease progression. In patients with chronic hepatitis C virus (HCV) infection, $CXCR3^+$ natural killer cells seem to be functionally impaired and therefore promote liver fibrosis[153]. In mice subjected to CCl_4 treatment, the antifibrotic activity of natural killer cells is lost during advanced stages of the disease, possibly owing to increased TGFβ production by HSCs[154].

Fibrogenic responses

Hepatic stellate cells and myofibroblasts. HSCs are the main effector cells during hepatic fibrogenesis[12]. Upon activation by profibrotic stimuli, they transdifferentiate into myofibroblasts[14], upregulate αSMA and produce collagen I and inhibitors of matrix degradation (Fig. 2), as well as pro-inflammatory cytokines and chemokines that will recruit immune cells to the site of inflammation[15]. Myofibroblasts show a contractile phenotype and can migrate to areas of active fibrogenesis where they are needed for wound contraction[14]. The transition of HSCs from a quiescent state to the activated, proliferative, motile myofibroblast state has a high energy demand and therefore includes a fundamental reprogramming of the cellular metabolic pathways[155,156].

It has been proposed that in mice, distinct subpopulations of HSCs exist, which are closely related but can exert distinct functions during chronic liver diseases[157]. New insights from scRNA-seq mouse studies reveal that quiescent HSCs represent a relatively homogeneous population, whereas activated HSCs can be subdivided into several distinct subpopulations[157,158]. In general, activated HSCs are characterized by high expression of ECM-related genes but differ in their capacity to produce inflammatory cytokines and chemokines. Interestingly, even fibrotic livers contain a population of HSCs with a resting (or probably weakly activated) phenotype that express various growth factors and cytokines and suppress liver inflammation and fibrosis[158,159]. By contrast, the highly activated or myofibroblastic HSCs promote liver fibrosis and hepatocarcinogenesis[159,160]. Consistent with that, in mouse models and patients with liver cirrhosis, the balance between HSC populations is skewed towards increasing myofibroblastic HSCs[159]. Gene expression analysis suggests that the myofibroblastic subpopulation is derived from resting cytokine-rich HSCs rather than representing two independent populations, and it seems plausible that this phenotype can also revert to quiescent stages[161].

Activation signals. HSCs can be activated by various signals, including cell–cell contact with macrophages, cytokines derived from activated immune cells and PAMPs or DAMPs[162]. Once activated, HSCs can induce autocrine signals that perpetuate their fibrogenic state. Using a single-nucleus RNA sequencing-based approach, 68 receptor–ligand interactions conserved between mouse and human NASH were found that constitute autocrine HSC signalling circuits in advanced fibrosis[163].

The best-studied soluble profibrotic factor to date is TGFβ. TGFβ is produced by infiltrating lymphocytes and monocytes, tissue-resident macrophages and damaged hepatocytes[164]. Engulfment of cell debris by macrophages further enhances their production of TGFβ[165]. TGFβ potently stimulates HSCs to transdifferentiate, and TGFβ signalling in HSCs induces the production of collagens, αSMA and connective tissue growth factor[166,167]. The type 3 cytokine, IL-17, derived from T_H17 cells and neutrophils, has a prominent role in activating TGFβ signalling pathways in HSCs as it induces upregulation of TGFβ receptor II and enhances activation of downstream kinases[120,168]. In addition, TGFβ

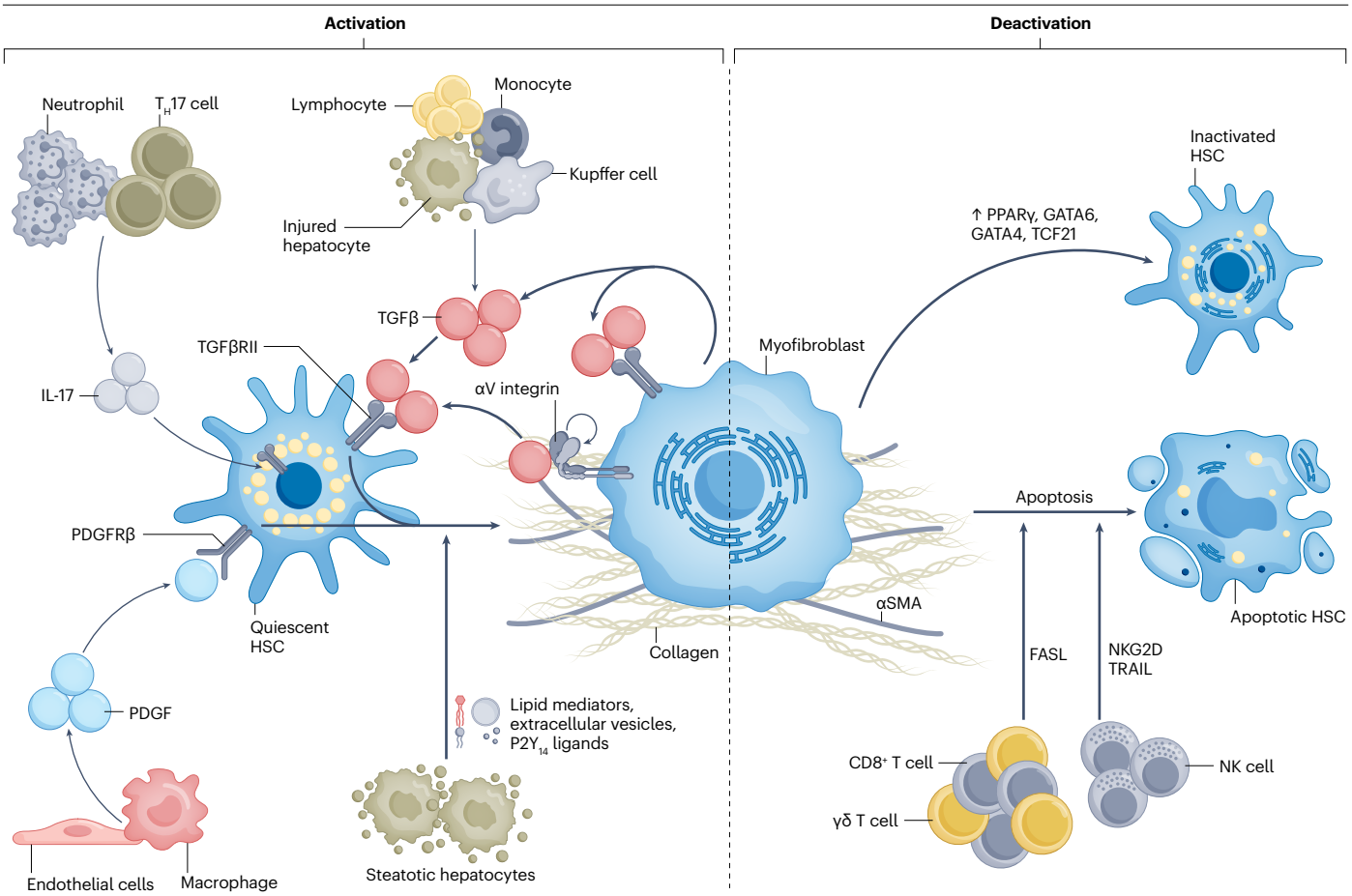

Fig. 2 | Activation and deactivation of HSCs. Hepatic stellate cells (HSC) have been shown to be the main effector cells during hepatic fibrogenesis. In the resting liver, they metabolize and store retinoids and are responsible for the turnover of the extracellular matrix. Upon activation by profibrotic stimuli, they transdifferentiate from quiescent HSC into myofibroblasts, lose their vitamin A, upregulate α-smooth muscle actin (αSMA) and start to produce collagen I. Transforming growth factor-β (TGFβ) is produced by infiltrating lymphocytes, monocytes, tissue-resident macrophages and damaged hepatocytes, and induces transdifferentiation of HSC. IL-17, produced by neutrophils and T helper 17 (T_H17) cells, sensitizes HSC to TGFβ stimulation through the upregulation of TGFβ receptor II (TGFβRII). Latent TGFβ binds to extracellular matrix proteins, rendering TGFβ inactive, and can be released via αV integrin-mediated contraction of activated HSC. Activated HSCs also produce TGFβ, perpetuating their activation in a feedforward loop. Platelet-derived growth factor (PDGF), produced by endothelial cells and macrophages, also induces HSC activation. Lipid mediators, danger signals and extracellular vesicles released by damaged hepatocytes further perpetuate HSC activation. Upon fibrosis resolution, HSC either die or revert to an inactive state, mediated through upregulation of the transcription factors peroxisome proliferator-activated receptor-γ (PPARγ), GATA-binding factor 4 (GATA4), GATA6 and transcription factor 21 (TCF21). Lymphocytes, such as natural killer (NK) cells, γδ T cells and $CD8^+$ T cells, can actively remove activated HSCs and myofibroblasts via induction of apoptosis.

can be deposited in the ECM (then called latent TGFβ) and activated at a later time through αV integrin-mediated HSC contraction[169]. Thus, deletion of the αv subunit in HSC prevents TGFβ activation and protects mice from hepatic fibrosis[170]. Activated HSCs also produce TGFβ, resulting in a feedforward loop perpetuating fibrogenesis[167]. A study published in 2021 demonstrated that TGFβ can also induce autophagy in HSCs[171]. Autophagy provides energy and nutrients critical for HSC activation through the breakdown of cellular components and organelles[155]; abrogation of autophagy in mouse HSCs prevents liver fibrogenesis[172].

Platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) have also been associated with profibrogenic functions. PDGF is produced by endothelial cells, macrophages and activated HSCs in liver diseases[162,173]. PDGF acts on HSCs via the PDGF receptor-β (PDGFRβ), which is increased during liver injury and promotes proliferation, migration and survival of these cells[174]. VEGF is produced by hepatocytes during experimental liver fibrosis, and also induces HSC activation and proliferation, resulting in increased production of ECM proteins and TGFβ[175].

During metabolic liver injury, toxic lipids can promote HSC activation via direct and indirect mechanisms. Accumulation of cholesterol and fatty acids leads to the release of hedgehog ligands and extracellular vesicles from hepatocytes resulting in HSC proliferation and ECM production[176,177]. In addition, cholesterol-laden hepatocytes are engulfed by liver-resident and infiltrating macrophages, causing inflammasome activation, production of pro-inflammatory cytokines and TGFβ, which further perpetuates liver inflammation, HSC activation and fibrogenesis[178,179]. Other lipid mediators associated with

HSC activation and fibrogenesis include lysophosphatidic acid and sphingosine-1-phosphate, which accumulate during NAFLD and NASH and correlate with disease severity[180,181].

Role of the matrix (matrisome) and mechanical forces. The liver matrisome, a term used to describe the ECM proteome, comprises the fibrillar ECM proteins, proteases and protease inhibitors that mediate ECM changes, and soluble mediators bound and retained by ECM proteins[182]. In fact, proteomic analysis of the ECM revealed over 150 distinct ECM proteins in healthy human liver[183] — the matrisome changes substantially during hepatic fibrogenesis. Besides the obvious deposition of collagen and other fibrillar proteins, the ECM can send signals to cells via surface receptors and influence cell–cell communication[184]. ECM remodelling is highly dynamic and can be observed early after liver injury in vivo, long before changes to the organ architecture become apparent[185–187]. These alterations affect the elasticity usually provided by the ECM, leading to increased organ stiffness and reduced hepatocyte proliferation[188]. Alongside altered biomechanical properties and microarchitecture, cirrhotic ECM is specifically enriched in proteins that favour epithelial to mesenchymal transition and TGFβ signalling of their surrounding cells[189]. As mentioned earlier, TGFβ binds to fibrillary ECM proteins, rendering it inactive, and the release of TGFβ from this complex requires mechanical forces arising through integrin-mediated cell contraction[169]. Increased stiffness of the ECM, as seen in fibrosis, enhances ECM resistance to these mechanical forces and, therefore, directly contributes to TGFβ activation[190]. The ECM also directly influences the transcriptomic profile and secretome of liver sinusoidal endothelial cells[191] and the infiltration of immune cells, as adhesion and transmigration of leukocytes to sites of inflammation or injury are mediated through ECM receptors on their surface[192], which has been shown in mice and in vitro. In addition, ECM molecules bind chemokines released from parenchymal cells and resident leukocytes after liver injury, creating a chemotactic gradient that directs immune cells to sites of injury[193,194].

Inflammation in fibrosis resolution

In general, evidence from preclinical studies, clinical trials and clinical observations suggests that fibrosis is reversible[9]. Fibrosis regression, partly even from an already compensated cirrhosis stage, has been well documented after effective treatment of viral hepatitis[9] and following bariatric surgery in 180 patients with NASH[195]. When the underlying liver injury is removed and inflammation subsides, HSCs can revert to a quiescent phenotype promoting degradation and clean-up of the ECM and removal of scar tissue, ultimately resulting in regeneration of normal parenchyma[196]. This is an active process shaped by immune cells and their mediators.

Deactivation of HSCs. Deactivation of HSCs during fibrosis regression occurs via reversal to a quiescent-like phenotype or complete removal of activated HSCs through apoptosis induction[161,197]. Reverted HSCs remain primed and are therefore able to react much more quickly to recurring fibrogenic stimuli. This 'inactive state' is characterized by downregulation of fibrogenic gene expression (for example, collagen I, αSMA and TIMP1) but not necessarily upregulation of all typical quiescence markers[161]. The deactivation of HSCs seems to be regulated by a variety of transcription factors (Fig. 2). In mouse models of liver fibrosis, HSC-specific deletion of GATA-binding factor 6 (GATA6) or peroxisome proliferator-activated receptor-γ (PPARγ) results in increased fibrogenesis and impaired fibrosis regression[198]. Similarly, augmenting PPARγ by pharmacological agonists seems to reduce liver fibrosis as shown in preclinical[199] and clinical studies[200,201]. Transcription factor 21 (TCF21) is expressed by HSCs in healthy liver and suppresses expression of the genes encoding collagen, PDGFRβ and αSMA[202]. Upon fibrosis induction, HSCs lose the expression of *Tcf21*, which is restored during fibrosis regression. GATA4 has also been implicated in HSC deactivation, as overexpression of *Gata4* promotes fibrosis regression in mice[203]. Lymphocytes can kill activated HSCs through the induction of apoptosis in a cell–cell contact-dependent manner. Specifically, hepatic γδ T cells, as well as tissue-resident memory $CD8^+$ T cells, induce HSC apoptosis via the FAS–FAS-ligand pathway[61,135], whereas natural killer cells kill HSCs via NKG2D and tumour necrosis factor-related apoptosis-inducing ligand-mediated pathways[204].

Inflammatory cell reorganization. As described above, macrophages are key drivers of hepatic inflammation and fibrosis, but they can also adopt a restorative phenotype and support tissue regeneration. This switch can be induced by neutrophils[95] or phagocytic stimuli[205] which lead to increased secretion of MMPs (for example, MMP9, MMP12 and MMP13) and enhanced matrix degradation[206–208]. Importantly, results from preclinical models have shown that these restorative macrophages share a common origin with pro-inflammatory and profibrotic macrophages, indicating that this might be an active process of phenotype conversion (or maturation) rather than representing an independent subset[205,209]. As mentioned above, MAIT cells seem to prevent the reprogramming towards restorative macrophages, which also had increased autophagic activity in experimental liver fibrosis[142]. Restorative macrophages also produce anti-inflammatory mediators, such as IL-10, and can induce apoptosis of pro-inflammatory macrophages[210].

Besides inducing a restorative phenotype in macrophages, neutrophils can also contribute to fibrosis regression directly by promoting fibrolysis and vascular regrowth[211,212]. In addition, in mouse models of NASH, extracellular vesicles released from neutrophils induced the downregulation of pro-inflammatory and profibrotic gene expression in hepatocytes via microRNA-223 (refs. 213,214).

$CD8^+$ T cells with a tissue-resident memory phenotype ($CD69^+CD103^-$) accumulate in the liver during the resolution phase in a dietary NASH mouse model and induce apoptosis of activated HSCs[135]. Consistently, depletion of these cells prolonged fibrosis resolution, whereas adoptive transfer limited fibrosis progression. Notably, $CD69^+CD8^+$ tissue-resident memory T cells can also be found in fibrotic areas of patients with NASH[135].

Therapeutic implications

So far, the development of efficient antifibrotic therapies has been challenging. Despite numerous promising preclinical studies, results often do not translate to human disease in clinical trials. The most successful antifibrotic therapy is the efficient treatment of the underlying liver disease, as shown by the effectiveness of HCV elimination by modern antivirals[5] and by the results in two clinical trials of bariatric surgery in 288 and 180 patients with fibrotic NASH[8,195]. Many pharmacological compounds are currently being investigated for the treatment of NAFLD[215], to resolve inflammation in NASH and/or induce fibrosis regression[216]. At present, interim analyses of two randomized controlled phase III clinical trials in patients with NASH (NCT02548351, NCT03900429) have shown the antifibrotic efficacy of the FXR agonist obeticholic acid and the thyroid hormone receptor-β (THRβ) agonist resmetirom, respectively, giving rise to the expectation that we will soon have a first 'antifibrotic compound' for the treatment of patients with liver disease

in the clinic[27]. However, substantial side effects (for example, pruritus, LDL cholesterol increase) and unclear long-term benefits (the study is currently ongoing to assess patient-related outcomes) prompted an FDA panel in May 2023 to vote against conditional approval of obeticholic acid to treat NASH[217]. In principle, novel therapeutic strategies aim at targeting distinct processes during disease development, mainly hepatocellular (metabolic) injury, liver inflammation, liver fibrogenesis and fibrosis resolution.

Targeting liver inflammation

The concept of anti-inflammatory therapeutics to disconnect hepatic injury from its detrimental consequences — inflammation and fibrosis — is intriguing[218]. Given the predominant role that monocytes and macrophages have in the pathogenesis of liver diseases, several strategies have been proposed to target these cells. Inhibition of the CCR2–CCL2 chemokine pathway, which is critical for the recruitment of pro-inflammatory monocytes to the injured liver, with several different compounds having been shown to reduce liver pathology in preclinical studies[219]. The dual CCR2–CCR5 inhibitor cenicriviroc showed anti-fibrotic efficacy signals in a phase IIb clinical trial in 289 patients[220], but beneficial effects could not be confirmed in a large phase III trial in 1,778 adults with NASH and liver fibrosis[221], so that further development was terminated[218]. Activation and pro-inflammatory signalling of macrophages can also be targeted. Inhibition of TLR4 or inflammasome activation demonstrated preclinical efficacy in mouse models but is currently not in late-stage development for the treatment of liver fibrosis[21,222]. The apoptosis signal-regulating kinase 1 (ASK1) inhibitor selonsertib, which targets the intracellular ASK1 inflammatory signalling cascade, showed antifibrotic effects in mouse models[223] but not in phase III clinical trials in patients with bridging fibrosis or compensated cirrhosis due to NASH (n = 808 and n = 883, respectively)[224]. Other approaches aim at enhancing anti-inflammatory signalling in macrophages. Nuclear receptors, such as PPARs, liver X receptors or FXR, can induce an anti-inflammatory polarization of macrophages[156,199]. The pan-PPAR agonist lanifibranor demonstrated antifibrotic efficacy in mouse models[199,225] as well as in a phase IIb trial in 247 patients with active NASH[201], prompting its further evaluation in a phase III clinical trial (NCT04849728)[226]. Very likely, the success of targeting inflammatory mechanisms in liver fibrosis will (partly) depend on simultaneously ameliorating the underlying disease driver[227], as suggested from animal models in which anti-inflammatory interventions in fibrotic NAFLD models were more effective in combination with metabolism-modifying drugs[228].

Furthermore, the aetiology of the underlying liver disease is an important factor that needs to be considered when developing novel treatment options. Most approaches described here target myeloid cells in NAFLD-associated and NASH-associated fibrosis, as this has become the predominant liver pathology without adequate treatment options worldwide[229], and macrophages have a major role in this disease. However, different cells might be preferentially targeted in other fibrotic liver diseases. In chronic HBV infection, for example, targeting dysfunction of T cells and other lymphocytes might be the most promising strategy to induce virus clearance and thereby reverse liver pathology[107,230,231]. This strategy could, however, also involve targeting macrophages, as Kupffer cell subsets can overcome the tolerogenic potential of the hepatic microenvironment by sensing IL-2 and cross-presenting hepatocellular antigens in mouse models of HBV infection, and could thereby boost (antiviral) hepatic T cell immunity[107]. T cells are also a major focus in the treatment of autoimmune hepatitis, but auto-aggressive effector T cell responses need to be better controlled and current strategies aim at augmenting the pool and function of T_{reg} cells[232,233]. In alcoholic liver disease (ALD), infiltration of neutrophils is a prominent feature correlating with inflammation and driving disease progression, and targeting neutrophil recruitment or function might therefore be explored for the treatment of ALD[93,234].

Targeting fibrogenesis and fibrolysis

Strategies targeting the process of fibrogenesis itself are usually directed at preventing or limiting HSC activation. Because of its prominent role in HSC activation, TGFβ might seem an obvious target. However, owing to its diverse systemic functions, pan-TGFβ blockade results in undesired effects such as autoimmunity[235], and several clinical trials investigating monoclonal antibodies against TGFβ had to be terminated owing to adverse events[1]. Instead, local or site-specific regulation of TGFβ might be more advisable. Integrins containing αV subunits can induce a transition of latent to active TGFβ in the ECM, and deletion of this subunit protected mice from fibrosis development in several organs[170]. Data on the efficacy of αV integrin inhibitors in patients are still lacking, but several compounds (such as the pan-αv-binding antibodies abituzumab and intetumumab or the αV integrin antagonist cilengitide) are currently in clinical development[236].

Like macrophages, HSCs also express various nuclear receptors, which induce antifibrotic effects when activated[237]. For example, the FXR agonists obeticholic acid and cilofexor can reduce liver fibrosis in mouse models[238,239], and a phase III trial of obeticholic acid including 1,968 patients with NASH demonstrated an improvement in liver fibrosis[240]. However, no FXR agonist is currently approved for the treatment of fibrosis in NASH, whereas obeticholic acid is used in clinical routine as a second-line therapy for patients with primary biliary cholangitis. As mentioned above, the pan-PPAR agonist lanifibranor also improved hepatic fibrosis in a clinical trial in 247 patients with NASH[201]. Preclinical studies have suggested that this effect is mediated via PPARγ agonism in HSCs and parallel PPARδ agonism in macrophages, resulting in reduced activation of both cell types[199]. Antifibrotic effects have also been reported for THR stimulation, and thyromimetic agents, which can be used to treat dyslipidaemia, are currently in clinical development for the treatment of NASH[241]. However, antifibrotic effects in HSCs are probably mainly mediated via THRα[156] and not via THRβ, the current target of thyromimetic agents in advanced clinical development[241].

Strategies to induce fibrosis regression with the removal of scar tissue and regeneration of normal parenchyma are also being actively investigated. To successfully stimulate fibrolysis, the underlying injury needs to be removed and inflammation resolved to facilitate the reversal of HSCs to a quiescent phenotype and degradation of the ECM[196]. This active and highly controlled process involves a finely tuned interaction between neutrophils and macrophages[242]. Macrophages can adopt a restorative phenotype, a switch that can be induced by neutrophils and/or phagocytic stimuli, and support tissue regeneration[95,205]. Pharmacological inhibition of pro-inflammatory monocyte recruitment with a CCL2 inhibitor was shown in mice to shift the balance of intrahepatic macrophages towards the restorative phenotype and thereby accelerate fibrosis regression[243]. Adoptive transfer of ex vivo differentiated restorative macrophages ameliorated hepatic fibrosis in mouse models and slightly reduced the model of end-stage liver disease score in a small phase I trial in nine patients with compensated liver cirrhosis[244–246]. Although this approach seemed safe in the small pilot trial in patients, the long-term stability of the macrophage phenotype and clinical efficacy remain to be seen. Mesenchymal stromal cells (MSCs)

have immunoregulatory properties and are also being explored for adoptive cell therapy[247]. The transfer of bone marrow-derived MSCs and MSC-derived extracellular vesicles reduced both inflammation and fibrosis in mouse models of liver disease, and clinical trials are underway[248]. The adoptive transfer of chimeric antigen receptor T cells that target senescent hepatocytes via the senescence-associated urokinase-type plasminogen activator receptor was also effective in preclinical models in reducing liver fibrosis[249].

Conclusions

The basic principles of liver inflammation have been known for decades. Continuous liver injury and hepatocyte cell death trigger inflammatory responses, which subsequently drive fibrogenesis by activating HSCs that transdifferentiate towards matrix-producing myofibroblasts. However, new technologies have emerged at a fast pace allowing a more comprehensive understanding of these processes. These technological advances include sophisticated mouse models (better reflecting human pathology), multicellular in vitro models, omics analyses of transcriptomes, proteomes, lipidomes and metabolomes on a single-cell level, and spatial and dynamic techniques[250–252]. Such current studies have revealed that the sequential concept – injury, inflammation, fibrosis – is oversimplified, as these processes are non-hierarchical but rather intertwined. Many pathogenic mediators – including cytokines, danger signals, microbial metabolites and bile acids – affect metabolism, injury, inflammation and fibrosis simultaneously. In addition, the cellular composition of parenchymal, non-parenchymal and immune cells in the liver is much more heterogeneous than previously anticipated and can change rapidly, so that cellular interactions and adaptations of cellular functions need to be cautiously interpreted with respect to the spatial organization within the (diseased) liver[253]. From these insights, a plethora of novel potential anti-inflammatory and antifibrotic targets have emerged[254]. It will be important to advance current diagnostic procedures in parallel for optimal translation of the currently obtained insights into the pathogenesis of liver inflammation and fibrosis to the clinic. For instance, a liver biopsy sample might be described not only using a semiquantitative scoring system on haematoxylin and eosin staining but also in terms of specific features of inflammation and fibrosis captured simultaneously to enable better patient stratification. This necessity has been demonstrated, for example, in severe alcohol-associated hepatitis, in which different histological patterns of immune cells (neutrophils versus $CD8^+$ T cells) relate to prognosis[93]. The overall close association of inflammation and fibrosis with patient-relevant end points in chronic liver diseases gives legitimate hope that the in-depth understanding of inflammatory and fibrogenic pathways will ultimately lead to the development of effective treatment.

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